

FORM PTO-1390
(REV. 11-2000)

U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

ATTORNEY'S DOCKET NUMBER

**TRANSMITTAL LETTER TO THE UNITED STATES
DESIGNATED/ELECTED OFFICE (DO/EO/US)
CONCERNING A FILING UNDER 35 U.S.C. 371**

0471-0260P

U.S. APPLICATION NO. (If known, see 37 CFR 1.5)

09/830449

INTERNATIONAL APPLICATION NO.

PCT/EP99/07887

INTERNATIONAL FILING DATE

October 18, 1999

PRIORITY DATE CLAIMED

October 30, 1998

TITLE OF INVENTION

A PROCESS FOR THE PREPARATION OF ALPHA-ARYLALKANOIC ACIDS

APPLICANT(S) FOR DO/EO/US

ALLEGRETTI, Marcello; CESTA, Maria Candida; MANTOVANINI, Marco; NICOLINI, Luca

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39 (1).
4. ☒ The US has been elected by the expiration of 19 months from the priority date (Article 31).
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
 - a. ☒ is transmitted herewith (required only if not transmitted by the International Bureau). WO 00/26176
 - b. ☒ has been transmitted by the International Bureau.
 - c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
 - a. ☐ is transmitted herewith.
 - b. ☐ has been previously submitted under 35 U.S.C. 154(d)(4)
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3)).
 - a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
 - b. ☐ have been transmitted by the International Bureau.
 - c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
 - d. ☒ have not been made and will not be made.
8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. ☐ An English language translation of the annexes of the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 20. below concern document(s) or information included:

11. ☒ An Information Disclosure Statement under 37 CFR 1.97 and 1.98-International Search Report (PCT/ISA/210) w/ 1 document
12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. ☒ A **FIRST** preliminary amendment.
14. ☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
15. ☐ A substitute specification.
16. ☐ A change of power of attorney and/or address letter.
17. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821-1.825.
18. ☐ A second copy of the published international application under 35 U.S.C. 154(d)(4).
19. ☐ A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).
20. ☒ Other items or information:
 - 1.) PCT Substitute Claims Letter w/ International Preliminary Examination Report (PCT/IPEA/409) and claim 1
 - 2.) PCT Request (PCT/RO/101)
 - 3.) Zero (0) sheets of Formal Drawings

U.S. APPLICATION NO (if known, see 37 CFR 1.5)		INTERNATIONAL APPLICATION NO		ATTORNEY'S DOCKET NUMBER	
09/830449		PCT/EP99/07877		0471-0260P	

<p>21. <input checked="" type="checkbox"/> The following fees are submitted:</p> <p>BASIC NATIONAL FEE (37 CFR 1.492(a)(1)-(5): Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO. \$1,000.00</p> <p>International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO \$860.00</p> <p>International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO. \$710.00</p> <p>International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4) \$690.00</p> <p>International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4). \$100.00</p> <p style="text-align: center;">ENTER APPROPRIATE BASIC FEE AMOUNT =</p> <p>Surcharge of \$130.00 for furnishing the oath or declaration later than <input type="checkbox"/> 20 <input checked="" type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(e)).</p> <table border="1" style="width:100%; border-collapse: collapse; font-size: small;"> <tr> <th style="width: 15%;">CLAIMS</th> <th style="width: 25%;">NUMBER FILED</th> <th style="width: 25%;">NUMBER EXTRA</th> <th style="width: 15%;">RATE</th> <th style="width: 20%;"></th> </tr> <tr> <td>Total Claims</td> <td>12 - 20 =</td> <td>0</td> <td>X \$18.00</td> <td>\$ 0</td> </tr> <tr> <td>Independent Claims</td> <td>2 - 3 =</td> <td>0</td> <td>X \$80.00</td> <td>\$ 0</td> </tr> <tr> <td colspan="3">MULTIPLE DEPENDENT CLAIM(S) (if applicable) Yes</td> <td>+ \$270.00</td> <td>\$ 270.00</td> </tr> <tr> <td colspan="4" style="text-align: right;">TOTAL OF ABOVE CALCULATIONS =</td> <td>\$ 1260.00</td> </tr> </table> <p><input checked="" type="checkbox"/> Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by 1/2.</p> <p style="text-align: right;">SUBTOTAL =</p> <table border="1" style="width:100%; border-collapse: collapse; font-size: small;"> <tr> <td>Processing fee of \$130.00 for furnishing the English translation later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(f)).</td> <td>\$ 0</td> </tr> <tr> <td style="text-align: right;">TOTAL NATIONAL FEE =</td> <td>\$ 630.00</td> </tr> <tr> <td>Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). \$40.00 per property +</td> <td>\$ 0</td> </tr> <tr> <td style="text-align: right;">TOTAL FEES ENCLOSED =</td> <td>\$ 630.00</td> </tr> </table> <table border="1" style="width:100%; border-collapse: collapse; font-size: small;"> <tr> <td style="width: 80%;"></td> <td style="width: 20%; text-align: center;">Amount to be:</td> </tr> <tr> <td></td> <td style="text-align: center;">refunded</td> </tr> <tr> <td></td> <td style="text-align: center;">charged</td> </tr> </table>	CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		Total Claims	12 - 20 =	0	X \$18.00	\$ 0	Independent Claims	2 - 3 =	0	X \$80.00	\$ 0	MULTIPLE DEPENDENT CLAIM(S) (if applicable) Yes			+ \$270.00	\$ 270.00	TOTAL OF ABOVE CALCULATIONS =				\$ 1260.00	Processing fee of \$130.00 for furnishing the English translation later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(f)).	\$ 0	TOTAL NATIONAL FEE =	\$ 630.00	Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). \$40.00 per property +	\$ 0	TOTAL FEES ENCLOSED =	\$ 630.00		Amount to be:		refunded		charged	<p>CALCULATIONS</p> <p>PTO USE ONLY</p>
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a. ☒ A check in the amount of \$ 630.00 to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account. No. _____ in the amount of \$ _____ to cover the above fees.
 A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any
 overpayment to Deposit Account No. 02-2448.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

Send all correspondence to:
Birch, Stewart, Kolasch & Birch, LLP or Customer No. 2292
P.O. Box 747
Falls Church, VA 22040-0747
(703)205-8000

Date: April 27, 2001

By #32,868
 Raymond C. Stewart, #21,066

/cqc

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09/830449

531 Rec'd PCT. 27 APR 2001

PATENT
0471-0260P

IN THE U.S. PATENT AND TRADEMARK OFFICE

Applicant: ALLEGRETTI, Marcello et al. Conf.:
Int'l. Appl. No.: PCT/EP99/07887
Appl. No.: New Group:
Filed: April 27, 2001 Examiner:
For: A PROCESS FOR THE PREPARATION OF
ALPHA-ARYLAKANOIC ACIDS

PRELIMINARY AMENDMENT

BOX PATENT APPLICATION

Assistant Commissioner for Patents
Washington, DC 20231

April 27, 2001

Sir:

The following Preliminary Amendments and Remarks are respectfully submitted in connection with the above-identified application.

AMENDMENTS

IN THE SPECIFICATION:

Please amend the specification as follows:

Before line 1, insert --This application is the national phase under 35 U.S.C. § 371 of PCT International Application No. PCT/EP99/07887 which has an International filing date of October 18, 1999, which designated the United States of America and was published in English.

Docket No. 0471-0260P

REMARKS

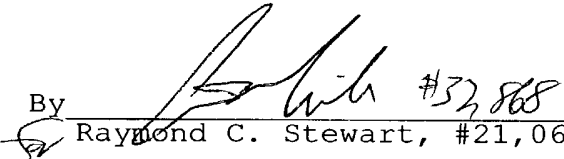
The specification has been amended to provide a cross-reference to the previously filed International Application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

Respectfully submitted,

BIRCH, STEWART, KOLASCH & BIRCH, LLP

By

 #32,868
Raymond C. Stewart, #21,066

RCS/cqc
0471-0260P

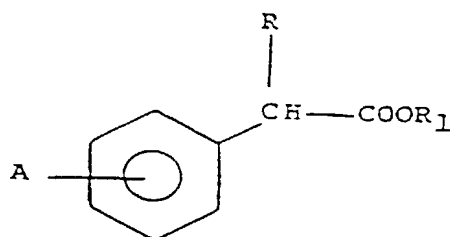
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(Rev. 02/12/01)

A PROCESS FOR THE PREPARATION OF ALPHA-ARYLALKANOIC
ACIDS

The present invention relates to a process for the preparation of meta or para-substituted α -arylalkanoic acids.

More particularly, the invention relates to a process for the preparation of compounds of formula (I)

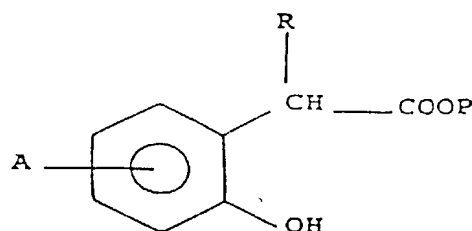


(I)

wherein:

R is hydrogen, C_1 - C_6 alkyl; R_1 is hydrogen, straight or branched C_1 - C_6 alkyl, phenyl, p-nitrophenyl, a cation of an alkali or alkaline-earth metal cation or of a pharmaceutically acceptable ammonium salt; A is C_1 - C_4 alkyl, aryl, aryloxy, arylcarbonyl, 2-, 3- or 4-pyridocarbonyl, aryl optionally substituted with one or more alkyl, hydroxy, amino, cyano, nitro, alkoxy, haloalkyl, haloalkoxy; A is at the meta or para positions;

starting from compounds of formula (II)



(II)

in which P is straight or branched C₁-C₆ alkyl, phenyl, p-nitrophenyl.

5 Different strategies are at present used for removing the phenolic hydroxyl of arylalkanoic acids derivatives, based on the derivatization and subsequent elimination of the derivative by reduction, but in most cases such procedures suffer from drawbacks such as high-cost reagents or lack of selectivity.

10 British Patent 2025397 (Chinoin), discloses the use of various derivatives of the phenolic hydroxyl, such as phenylaminocarbonyl, 1-phenyl-5-tetrazolyl, 2-benzoxazolyl, -SO₂OMe, and the reduction of the derivative with hydrogen on Pd/C catalyst.

15 WO 98/05632 application, in the Applicant's name, discloses the use of perfluoroalkanesulfonates, in particular trifluoromesylate, followed by reduction with formic acid and triethylamine in the presence of palladium acetate / triphenylphosphine complex.

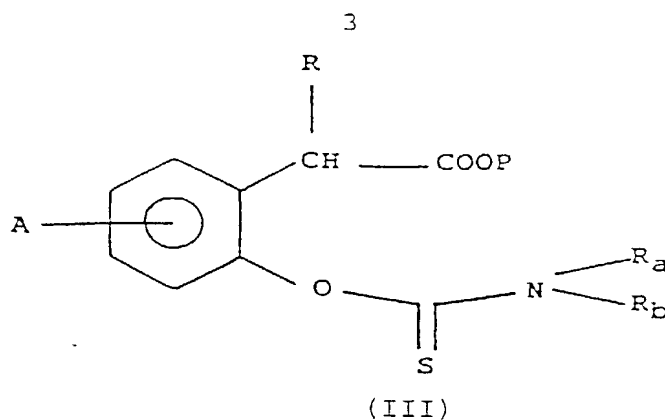
20 It has now been found a process for the preparation of arylpropionic acids starting from the corresponding α -hydroxylated derivatives, using inexpensive reagents and keeping intact any reducible groups, such as esters or ketones, present on the side chains of the starting molecules.

25 According to the process of the invention, the compounds of formula (I) are prepared through the following steps:

30 a) transformation of compounds of formula (II) into compounds of formula (III):

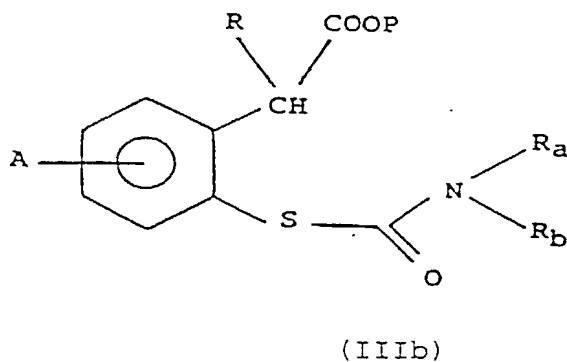
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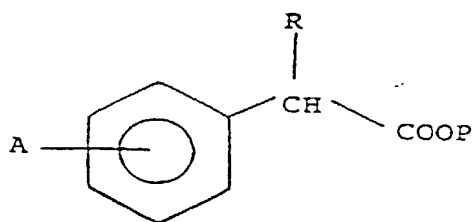


wherein R_a and R_b are C₁-C₆ alkyl, preferably methyl;

- 10 b) thermal rearrangement of compound (III) to give (IIIb)

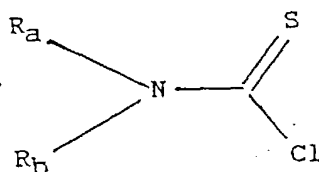


- 20 c) catalytic hydrogenation of (IIIb) to give (IIIc)



- d) transformation of (IIIc) into (I).

30 The compounds of formula (II) can be prepared as described in WO 98/05623. Briefly, starting from arylolefins of formula (IV)



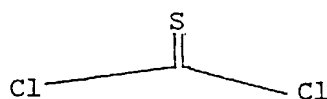
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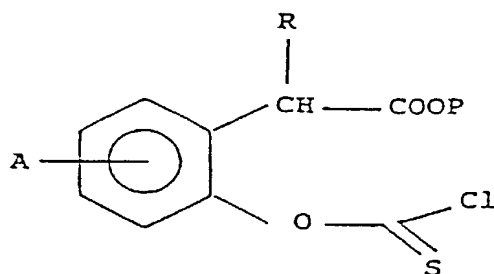
wherein R_a and R_b are as defined above, in the presence of an inorganic base such as an alkali or alkaline-earth carbonate, or an organic one, such as triethylamine or pyridine.

5 Alternatively, compound of formula (II) is reacted first with thiophosgene,



10

to obtain compound (IIIa)



15

20

(IIIa)

which is subsequently reacted with HNR_aR_b in which R_a and R_b are as defined above.

25 The conversion of the phenol in O-aryl-dialkylthiocarbamate by reaction with $\text{R}_b\text{R}_a\text{NCSCl}$, and the subsequent thermal rearrangement (step b) of the O-aryl-dialkylthiocarbamate to give compound (IIIb), are described in Newman and Karnes, "The conversion of phenols", J. Org. Chemistry, Vol. 31, 1966, 3980-3982.

30

On the other hand, as for the preparation of the O-aryl-dialkylthiocarbamate by reacting the phenol with

thiophosgene and subsequently the resulting product with amine R_aR_bNH , the method reported in Can. J. Chem., 38, 2042-52 (1960) can be followed.

5 In step c), the catalytic hydrogenation of S-aryl-dialkylthiocarbamate (IIIb) to give (IIIc) can be carried out with Ni-Raney as catalyst.

Compound (IIIc) is easily converted to (I) through conventional procedures for the hydrolysis of the ester group and optional subsequent reesterification or
10 salification of the carboxylic group.

The process of the invention proved to be particularly advantageous when group A in general formula (I) is an optionally substituted aroyl group, in that the carbonyl function is preserved during the
15 reduction of the thiocarbamoyl derivative. For example, when A is benzoyl, no reduction of the ketone under the used experimental conditions is observed. Furthermore, as already mentioned, the process of the invention is based on the use of low cost reagents, provides good
20 yields, requires no purifications of the intermediates and has a low environmental impact.

The following examples illustrate the invention in greater detail.

Example 1

25 Preparation of 2-(3'-benzoyl-2'-hydroxyphenyl)-propionic acid methyl ester (2)

A solution of 2-(3'-benzoyl-2'-acetoxyphenyl)propionic acid (1) (6.2 g) in methanol (35 ml) was added with concentrated H_2SO_4 (0.3 ml). The mixture was
30 stirred at room temperature for 15 hours until disappearance (1) and of the reaction intermediates. The solvent was evaporated off under vacuum and the residue

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was dissolved in ethyl acetate (30 ml) and washed with water. The organic layer was treated with a NaOH solution (100 ml), and the basic phase was acidified with 4N HCl and extracted with ethyl acetate (2 x 25 ml). The collected organic layers were washed with brine, dried over Na₂SO₄ and evaporated under vacuum. The crude product (4.3 g) was dissolved in isopropyl ether (5 ml) and the slightly yellow precipitate was filtered. n-Hexane (25 ml) was added to the residue and the mixture was stirred overnight. After filtration, 3.2 g of (2) were obtained (0.11 mol; 70% yield starting from 4) as a whitish solid (melting point 108-111°C).

TLC (CH₂Cl₂/MeOH 9:1 R_f = 0.45)
Elementary analysis calculated for C₁₇H₁₆O₃ : C-71.81, H-5.67.

Found: C-71.16, H-5.63.

¹H-NMR (CDCl₃) δ 8.4 (s, OH, 1H); 7.85-7.3 (m, 7H); 7.0 (d, 1H, J = 7 Hz); 3.95 (q, 1H, 8 Hz); 3.8 (s, 3H); 1.6 (d, 3H, J = 8 Hz).

20 Example 2

Preparation of 2-(3'-benzoyl-2'-O-dimethylthiocarbamoylphenyl)-propionic acid methyl ester (3)

A solution of (2) (3.2 g, 0.011 mol) in acetone (25 ml) was added with potassium carbonate (1.65 g, 0.012 mol) and the mixture was stirred at room temperature for 15 min. A solution of N,N-dimethylcarbamoyl chloride (1.51 g, 0.012 mol) in acetone (5 ml) was added drop by drop to the refluxed mixture for 2 hours. After cooling at room temperature, the precipitated inorganic salts were filtered off and the solvent was evaporated under vacuum. The residue was dissolved in ethyl acetate (25 ml) and washed with water (2 x 10 ml) and brine (2 x 10

8

ml). The organic phase was dried over Na_2SO_4 and evaporated under vacuum, to obtain 3.45 g of (3) as a dark oil sufficiently pure to be used in the subsequent step.

5 TLC (n-hexane/EtOAc 8:2) R_f = 0.25

Elementary analysis calculated for $\text{C}_{20}\text{H}_{22}\text{NO}_4\text{S}$: C-64.49, H-5.95, N-3.76, S-8.61.

Found: C-64.17, H-5.92, N-3.82, S-8.60.

10 ^1H -NMR (CDCl_3) δ 7.95-7.8 (m, 4H); 7.6-7.4 (m, 3H); 7.2 (d, 1H, J = 7 Hz); 3.9 (q, 1H, J = 8 Hz); 3.7 (s, 3H); 3.6 (s, 3H); 3.4 (s, 3H) 1.6 (d, 3H, J = 8 Hz).

Example 3

Preparation of 2-(3'-benzoyl-2'-S-dimethylthiocarbamoylphenyl)propionic acid methyl ester (4)

15 Compound (3) (3.45 g) was heated in a flask at T = 210°C (temperature of the outer oil bath) for 2 hours under stirring. After cooling at room temperature and evaporation under vacuum, 3.45 g of (4) were obtained (0.0054 mol) sufficiently pure to be used without
20 further purifications.

TLC (n-hexane/ethyl acetate 8:2 R_f = 0.2).

Elementary analysis calculated for $\text{C}_{20}\text{H}_{22}\text{NO}_4\text{S}$: C-64.49, H-5.95, N-3.76, S-8.61.

Found: C-64.17, H-5.92, N-3.82, S-8.60.

25 ^1H -NMR (CDCl_3) δ 7.9-7.8 (m, 3H); 7.7-7.3 (m, 5H); 4.4 (q, 1H, J = 8 Hz); 3.65 (s, 3H); 3.2-2.9 (d broad, 6H); 1.6 (d, 3H, J = 8 Hz).

Example 4

Preparation of 2-(3'-benzoylphenyl)-propionic acid methyl ester (5)

30 Acetone (50 ml) was added to Ni-Raney (50% in water, 20 ml) and the water/acetone mixture was removed.

Elementary analysis calculated for $C_{16}H_{14}O_3$: C-75.57,
H-5.55.

Found: C-75.19, H-5.53.

5 $^1\text{H-NMR}$ (CDCl_3) δ 7.91-7.75 (d, 3H), 7.74-7.51 (m, 2H),
7.50-7.35 (m, 4H), 3.85 (q, 1H, $J = 10$ Hz), 1.58 (d, 3H,
 $J = 10$ Hz).

Druckexemplar

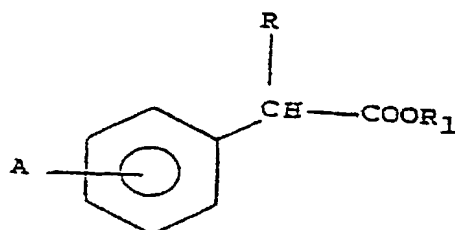
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PCT/EP99/07887

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CLAIMS

1. A process for the preparation of meta or para-substituted α -arylalkanoic acids of formula (I):



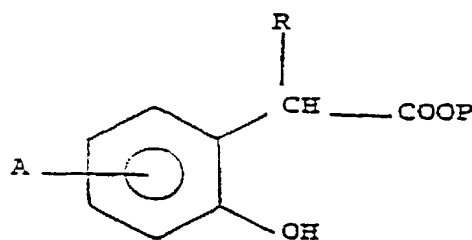
(I)

wherein:

R is hydrogen, C_1 - C_6 alkyl; R_1 is hydrogen, straight or branched C_1 - C_6 alkyl, phenyl, p-nitrophenyl, a cation of an alkali or alkaline-earth metal cation or of a pharmaceutically acceptable ammonium salt; A is C_1 - C_4 alkyl, aryl, aryloxy, arylcarbonyl, 2-, 3- or 4-pyridocarbonyl, aryl optionally substituted with one or more alkyl, hydroxy, amino, cyano, nitro, alkoxy, haloalkyl, haloalkoxy; A is at the meta or para positions;

which process comprises the following steps:

a) transformation of compounds of formula (II)



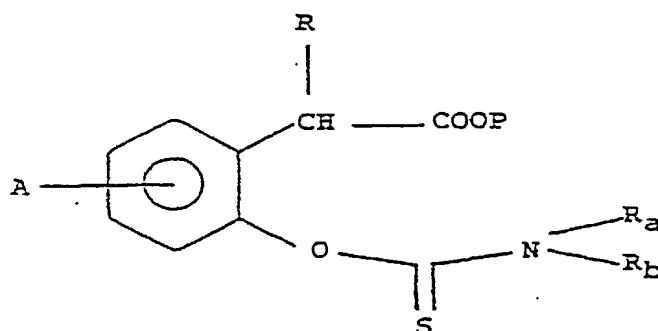
(II)

in which P is straight or branched C_1 - C_6 alkyl, phenyl, p-nitrophenyl,

WO 00/26176

PCT/EP99/07887

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into compounds of formula (III)

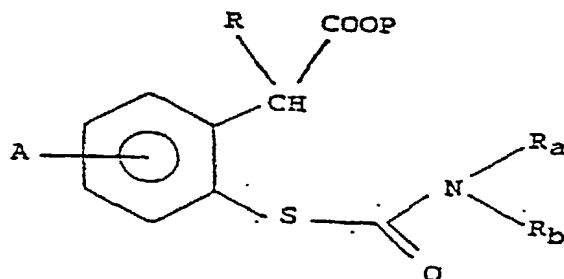


(III)

wherein

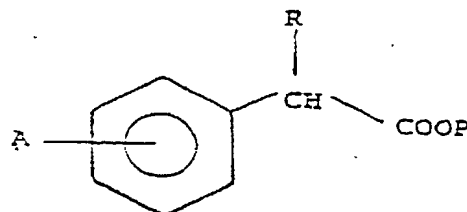
R_a and R_b are C₁-C₆ alkyl, ~~preferably methyl,~~

15 b) thermal rearrangement of compound (III) to give (IIIb)



(IIIb)

25 c) catalytic hydrogenation of (IIIb) to give (IIIc)



(IIIc)

d) transformation of (IIIC) into (I).

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4. A process as claimed in claim 1, in which the transformation of step a) is carried out by reaction of compound (II) with thiophosgene

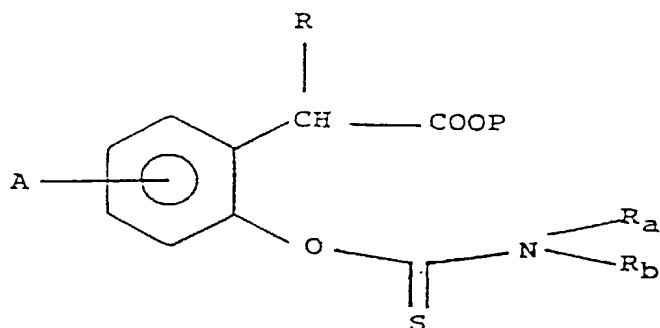
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30

7. As a reaction intermediate, the compound

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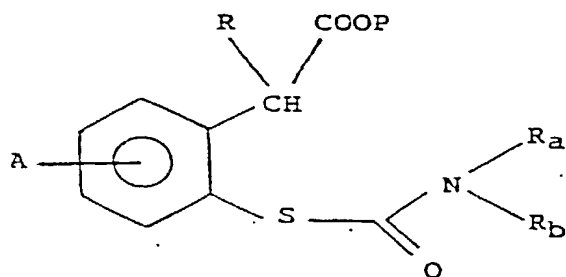


(III)

wherein:

R is hydrogen, C_1 - C_6 alkyl; A is a C_1 - C_4 alkyl, aryl, aryloxy, aryl optionally substituted with one or more alkyl, hydroxy, amino, cyano, nitro, alkoxy, haloalkyl, haloalkoxy, A is at the meta or para positions; P is straight or branched C_1 - C_6 alkyl, phenyl, p-nitrophenyl; R_a and R_b are C_1 - C_6 alkyl.

8. As a reaction intermediate, the compound



(IIIb)

wherein A, R, P, R_a and R_b are as defined in claim 7.

PCT

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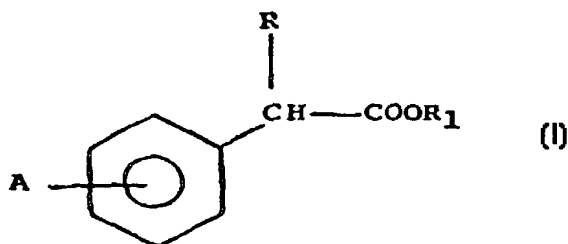
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(54) Title: A PROCESS FOR THE PREPARATION OF ALPHA-ARYLALKANOIC ACIDS

(57) Abstract

A process for the preparation of meta or para-substituted α -arylalkanoic acids of formula (I) wherein R and R₁ are as defined in the disclosure.





Attorney Docket No. 0471-0260P

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A PROCESS FOR THE PREPARATION OF ALPHA-ARYLALKANOIC ACIDSFill in Appropriate
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the specification of which is attached hereto. If not attached hereto,
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and amended on April 27, 2001 (if applicable) and/or
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International Application Number PCT/EP99/7887; and was
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<u>MI98A002332</u> (Number)	<u>Italy</u> (Country)	<u>October 30, 1998</u> (Month/Day/Year Filed)	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
_____ (Number)	_____ (Country)	_____ (Month/Day/Year Filed)	<input type="checkbox"/> Yes	<input type="checkbox"/> No
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Attorney Docket No. 0471-0260P

I hereby appoint the practitioners at CUSTOMER NO. 2292 as my attorneys or agents to prosecute this application and/or an international application based on this application and to transact all business in the United States Patent and Trademark Office connected therewith and in connection with the resulting patent based on instructions received from the entity who first sent the application papers to the practitioners, unless the inventor(s) or assignee provides said practitioners with a written notice to the contrary:

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Full Name of Fifth
Inventor, if any:
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Full Name of Sixth
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